REMARKS

Reconsideration of the application is respectfully requested. Claims 1-10 and 13-111 are pending in the application. Claims 3, 6, 7, 13, 15, 16, 36-50, 57-62, 69-98, and 108-110 have been withdrawn from consideration. Therefore, the only claims at issue are claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, 99-107, and 111. Claims 46 and 52 have been amended to correct typographical errors. No new matter has been added.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, 99-107, and 111 have been rejected under 35 U.S.C. §112, first paragraph, as lacking written description support with respect to the step of selective enzymatic acylation step. The Examiner contends that while the claims cover the use of any enzyme to perform the selective acylation, the specification only exemplifies Novozyme® 435. The Examiner also states that the claimed "mutants and variants" lack written description support because no sequence information is provided in the specification for these derivative enzymes nor are any of these derivative enzymes employed in an example.

The rejection is traversed, and reconsideration is respectfully requested.

First, the Examiner is respectfully reminded that working examples are not required in a patent application. *See* MPEP §2164.02; *In re Strahilevitz*, 668 F.2d 1229, 1232 (CCPA 1982) ("as acknowledged by the board, examples are not required to satisfy section 112, first paragraph"). Rather, the dispositive issue is whether the disclosure in the application is sufficient to convey to those of ordinary skill in the art that the inventors were in possession of the claimed invention at the time the application was filed. MPEP §2163.02. Here, the Examiner has acknowledged that the specification provides an extensive and detailed description of how enzymatic acylation is carried out according to the present invention. *See* Office Action, p. 10. This includes a description of suitable acylating enzymes, and specific examples of such enzymes, including *Pseudomonas sp.* lipoprotein lipase, *Candida antartica* lipase B, Novozyme® 435, and LipoZyme™ TL IM (p. 17, lines 8-20; p. 18, lines 6-23). It is improper for this disclosure to be ignored simply because it is not provided in a working example. Moreover, one of ordinary skill would have understood from

reading the specification that the inventors possessed the claimed method of separating enantiomers at the time the present application was filed, including the step of selectively acylating a racemic compound using one of the claimed acylating agents and any suitable acylating enzyme.

Additionally, working examples of the claimed mutant and variant enzymes are likewise not required in the application. Furthermore, sequence information is not needed to show that the inventors were in possession of these derivative enzymes because their sequences can be determined based on the parent enzyme. According to the specification, the claimed method can be performed using enzymes having an amino acid sequence that is more than 60% identical to one of the following enzymes, each of which has a known or routinely determinable amino acid sequence: *Pseudomonas sp.* lipoprotein lipase, *Candida antartica* lipase B, and *Thermomyces lanuginosus* lipase (p. 17, line 27 to p. 18, line 4). It is neither required nor encouraged for an application to include information that is already known in the art and/or easily determinable by those of ordinary skill. *See, e.g.*, *Falkner*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) ("[A] patent need not teach, and preferably omits, what is well known in the art.") (quoting *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987)); *S3 Inc. v. nVIDIA Corp.*, 259 F.3d 1364, 1376 (Fed. Cir. 2001) ("patents are written for and by skilled artisans"). Here, the inventors have identified the minimum percent homology needed for mutants and variants of certain known enzymes to function in the claimed method. Additional information, such as working examples and amino acid sequences, is unnecessary to establish that the inventors were in possession of these derivative enzymes at the time the application was filed.

Given the foregoing, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, 99-107, and 111 have been rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of U.S. Patent No. 6,551,806 ("Sturmer") and U.S. Patent No. 5,219,743 ("Takano"). Boegesoe is cited by the Examiner as disclosing a racemic diol that reacts with an enantiomerically pure acid derivative, after which HPLC separation is used to isolate the corresponding enantiomer of the acid-derived

intermediate. The Examiner acknowledges that Boegesoe teaches neither enzymatic acylation with a hydrolase enzyme to prepare the S- or R-diol of formula (II) nor the solvent of the present invention. Sturmer is cited by the Examiner as disclosing polymers that contain enzymes (e.g., hydrolases) and are used for enantioselective acylation of alcohols. Takano is cited by the Examiner as disclosing a method for optical resolution of Corey lactone diols using an acylating agent in the presence of an enzyme and any organic solvent that does not inactivate the enzyme. From this, the Examiner concludes that it would have been obvious to prepare the claimed S- or R-diol by subjecting Boegesoe's racemic diol mixture to selective enzymatic acylation using an acylating agent, an enzyme and any suitable solvent because such a method involves known compounds and a known chemical process that would allegedly yield predictable results.

The rejection is traversed, and reconsideration is respectfully requested.

According to the Examiner, Boegesoe teaches a process in which S- or R-citalopram is separated from its racemic mixture (Office Action, p. 10 citing Boegesoe at col. 3, Reaction Scheme I). This is incorrect because, *inter alia*, Boegesoe's Reaction Scheme I does not disclose a racemic mixture of citalopram. Rather, the reaction begins with a racemic mixture of an intermediate diol. The diol then forms an S- or R-esterified derivative upon reaction with an enantiomerically pure (S- or R-) acid. This acid-derivative is then reacted to form S- or R-citalopram.

The Examiner also contends that the pending claims encompass the Boegesoe reaction (which includes formation of an enantiomeric esterified derivative prior to formation of the desired enantiomeric product) by virtue of the term "comprising" in the claims. According to the Examiner's interpretation, this term allows the claim to cover additional, unrecited process steps, including those found in Boegesoe's reaction scheme. Contrary to the Examiner's interpretation, the claimed process does not in fact allow for the formation of an esterified derivative because claim 1 expressly requires the enzymatic acylation to form a specific mixture that does not contain an esterified derivative. More specifically, step (a) of claim 1 forms a mixture of the starting material of formula (II) in either the R- or S- form and the opposite enantiomer of a compound of formula (IV); and step (b) alternatively forms a mixture of deacylated compound of formula (II) and the acylated starting material of formula (IV) in the opposite enantiomer. Neither formula (II) nor formula (IV) is an ester. Hence, since the claimed method does not include formation of a mixture

containing an an esterified derivative prior to formation of the desired enantiomeric product, Boegesoe's reaction scheme necessarily falls outside the scope of the claims.

Regarding Sturmer, the Examiner acknowledges that the claimed diol of formula (II) has a significantly different structure than any starting substrate disclosed in Sturmer. *See* Office Action, p. 11. Nevertheless, the Examiner cites Sturmer as broadly teaching an enzymatic acylation that can be used to separate the enantiomers of any racemic alcohol. It appears that the Examiner is relying on an unreasonably broad interpretation of Sturmer. Notably, none of the exemplary compounds listed in Sturmer is a diol, and the only generic suggestion of diols is found in Sturmer's use of the phrase "polyhydric alcohols" (col. 11, lines 55-56). Further, Sturmer indicates that there are some restrictions on the types of alcohols that are suitable for use in its process, but gives no guidance as to what those restrictions might be. Given the foregoing, one of ordinary skill in the art reading Sturmer would not have reasonably concluded that Sturmer's process could be used to successfully separate enantiomers of any and all racemic alcohols, regardless of their structural complexity or other chemical and physical properties. On the contrary, there is simply too little disclosure in Sturmer and too much unpredictability in the field for a skilled artisan to have reached such an expansive conclusion.

In summary, the Examiner appears to be relying on impermissible hindsight to reconstruct the present invention when the combined disclosures in the cited references would not have reasonably led one of ordinary skill to predict that Sturmer's method could be successfully used to prepare the S- or R-enantiomer of Boegesoe's racemic diol. Rather, the claimed method was discovered as a result of the inventors' "intensive investigations" (*see* Specification at p. 21, lines 23-28). Moreover, the cited references would not have led one of ordinary skill to specifically select the claimed intermediate diol of formula II (as opposed to any other intermediate useful in the preparation of citalopram) for selective enzymatic acylation according to the claimed method.

Given the foregoing, claims 1, 2, 4, 5, 8-10, 14, 17-35, 51-56, 63-68, 99-107, and 111 are not obvious over the cited references. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 6, 2009

Respectfully submitted,

By Dianna Goldenson

Dianna Goldenson
Registration No.: 52,949
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant